

2017 ACR/EMA Revised Criteria for too Early Diagnosis of Granulomatosis with Polyangiitis (GPA)

Iraj Salehi-Abari

Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Granulomatosis with polyangiitis (GPA) or Wegener's granulomatosis is a systemic necrotizing vasculitis with small sized vessel involvement and granulomatous inflammation of ENT and/or Lung and/or Kidney that is associated with ANCA positivity.

Upon the clinical/laboratory/imaging judgement of an expert Rheumatologist in cooperation with an expert otolaryngologist and an expert infectious disease specialist the diagnosis of GPA can be established.

There have been three criteria for GPA including:

- The 1990 ACR classification criteria for Wegener's granulomatosis
- The EMA diagnostic criteria of systemic GPA
- Iran criteria for early diagnosis of GPA

The 1990 ACR criteria is not sensitive enough and it can not detect the cases of GPA in early stages.

The EMA criteria has been made for diagnosis of systemic GPA in the absence of biopsy and its sensitivity is too much low.

Iran criteria for early diagnosis of GPA is highly sensitive but there is a lag period of about a few months between the initial presentation of disease and the time of confirmation of it.

You have to know that with a little changes within Iran criteria a new criteria is created by the author of this letter called 2017 ACR/EMA revised criteria by which the diagnosis of GPA can be established too earlier with a lag period of a few weeks only.

Keywords: GPA; 1990 ACR Criteria; EMA Criteria; Iran Criteria; 2017 ACR/EMA Revised Criteria

***Corresponding Author:** Iraj Salehi-Abari, Associate professor, Rheumatology Research Center, Amir Alam Hospital, Tehran University of Medical Sciences, No 29, 6th Alley, Ghaem-magham St., P.O. Box 1586858111, Tehran, Iran; E-mail: salehiabari@sina.tums.ac.ir

Letter to Editor

Granulomatosis with polyangiitis is a systemic necrotizing vasculitis with small sized vessel involvement and granulomatous inflammation of ENT and/or Lung and/or Kidney that is associated with ANCA positivity [1, 2].

Its previous name was Wegener's granulomatosis that in January 2011 it was changed to Granulomatosis with polyangiitis abbreviated as GPA [3].

The prevalence of GPA is about 3 in 100,000. The peak age at onset in GPA is fourth and fifth decade but 15% of cases have the ages at onset less than 19 [4].

Almost all (>90%) cases of GPA are white [5]. We have to know that; the early diagnosis of GPA and then early treatment of it can result in a complete remission. The delay from onset to the time of diagnosis in GPA ranges from 2 to 20 months [6].

The clinical triad of GPA is including [7]:

- ENT involvement
- Lung involvement and
- Kidney involvement

The initial presentations of GPA are including:

- ENT: most often (84-100%)[8]
- Lung: may be
- Kidney: sometimes

Nose involvements are including: nasal crusting, rhinitis, nasal obstruction, runny nose, smell disturbances, purulent/bloody nasal discharge, epistaxis, nasal ulcer, severe nasal pain, nasal septal perforation and saddle-nose deformity.

Sinusitis is the most common initial presentation (# 70%) and clinical feature of GPA and chronic rhinosinusitis is the classic ENT finding in this disease [9].

In each one of below atypical sinusitis (AtS) if there is not any better explanation for it in the patient, we have to evaluate him/her for GPA [4].

- Recurrent sinusitis
- Chronic/intractable sinusitis
- Sinusitis along with sinus mass
- Sinusitis along with rhinitis
- Sinusitis along with otitis
- Sinusitis along with orbital cellulitis
- Sinusitis along with dacryocystitis
- Sinusitis along with mastoiditis
- Sinusitis with severe pain in the nose and
- Pansinusitis

We have to know that recurrent sinusitis is defined as more than 3 episodes of the sinusitis in a season and chronic/intractable sinusitis is a sinusitis with unresponsiveness to more than 3 weeks of antibiotic therapy [10].

AtS can be occurred due to opportunistic bacterial infections and/or fungal infections especially Mucormycosis but secondary to an underlying disease/state such as diabetic ketoacidosis, advanced complicated diabetes mellitus, malignancies, hereditary and/or acquired immunodeficiency states, organ transplantation especially bone marrow transplantation, chronic high dose corticosteroid therapy, chemotherapy/cytotoxic therapy and so on. It needs to be mentioned that one out of four cases with AtS can be the patient with GPA [4].

Ear involvements are including: otitis media in which serous otitis media is more common than purulent otitis media, hearing loss in which conductive hearing loss is more common than sensory-neural type, mastoiditis and vertigo [11].

In below pictures of otitis media if there is not any better explanation for it in the patient the same as AtS, we have to evaluate him/her for GPA.

- Persistent/intractable otitis media
- Recurrent otitis media
- Bilateral otitis media
- Otitis media with sensory-neural hearing loss
- Otitis media along with rhinitis and

- Otitis media with mastoiditis

It needs to be mentioned that; persistent otitis media is persistence of the disease during antibiotic therapy and/or relapse of the disease within one month of completion of antibiotic therapy. Recurrent otitis media is defined as recurrence of the disease for ≥ 3 episodes in 6 months or ≥ 4 episodes in 12 months [12].

We have to know that recurrent bilateral serous otitis media is the classic ear involvement in this disease [13].

Oral necrotic ulcer as the classic feature and strawberry gum hyperplasia as the pathognomonic picture of GPA can be seen in the mouth [14].

Ophthalmic involvements of GPA are divided into:

- Global involvements
- Orbital involvements

Ophthalmic global involvements are including; conjunctivitis, epi/scleritis, keratitis, corneal ulcer, uveitis, retinal vasculitis and so on.

Ophthalmic orbital involvements are including; proptosis, dacryocystitis, excessive tearing and ophthalmoplegia [15-17].

When we see all of above items in the eyes it is called “Red eye syndrome” or “blood shot eye”.

Laryngotracheal involvement are including hoarseness and stridor due to upper airway obstruction especially subglottic stenosis. Sometimes, subglottic stenosis is the only initial presentation of GPA [18, 19].

Lung involvement may be asymptomatic or in opposite side will be including hemoptysis or even acute and fulminant alveolar hemorrhage with respiratory failure.

In the chest X-Ray and/or High Resolution CT scan (HRCT) of lungs; nodules, cavities and fixed infiltrations are the most important findings [20, 21]. It needs to be mentioned that in the cases with pneumonia with below patterns we have to think about the diagnosis of GPA if there is not any better explanation for it the same as AtS.

- Intractable pneumonia
- Recurrent pneumonia
- Multiple lobe pneumonia
- Cavitate pneumonia
- Fleeting pneumonia
- Hemorrhagic pneumonia and
- Pneumonia along with sinusitis

Renal involvements are including microscopic hematuria and/or RBC casts and/or proteinuria and/or Azotemia with pathology of focal/diffuse segmental/crescentic necrotizing pauci-immune glomerulonephritis.

Renal involvement can vary from asymptomatic to vigorous azotemia/uremia due to rapidly progressive glomerulonephritis. In most cases with GPA; glomerulonephritis is not associated with immune complex depositions but, sometimes, interstitial nephritis and/or vasculitis and/or granulomatous inflammation are the only pathologic findings in kidney [22, 23].

Nowadays the GPA can be divided into two types:

- Limited GPA: (ENT± Lung) involvement
- Systemic GPA: [(ENT± Lung)+ Kidney] involvement

With ENT and/or lung involvement GPA is of limited type. Whereas with ENT and/or lung involvement along with kidney involvement we have GPA of systemic type. There is not any gender tendency in systemic GPA but limited GPA can be seen in women more than men.

Musculoskeletal manifestations of GPA are including [24]:

- Arthralgia/Arthritis
- Myalgia/Myopathy

Arthritis is the feature of GPA in less than one-third of cases can be presented as symmetric polyarthritis of small and large joints in both upper and lower limbs with positive RF (Rheumatoid arthritis like) or asymmetric oligoarthritis of large joints in lower limbs (Reiter's syndrome like) or acute migratory polyarthritis (Acute Rheumatic Fever like).

Skin manifestations are including; palpable purpura, ulcer, nodule, papule, vesicle, urticaria, livedoreticularis, erythema nodosum and pyoderma gangrenosum. In overall skin involvement can be presented as Leukocytoclastic vasculitis with or without hemorrhagic blister [25].

Neurologic involvements of GPA are including polyneuropathy, mononeuritis multiplex, cranial neuropathies (cranial nerves 2, 6, 7,...), cerebro-vascular accident, headache due to meningeal inflammation, and rarely CNS mass and even diabetes insipidus [26].

Gastro-intestinal (GI) involvement of GPA can be asymptomatic but enterocolitis with the presentations of abdominal pain and diarrhea, GI bleeding, ulcer, perforation, cholecystitis, ascites, pancreatitis, pancreatic mass and perianal ulcer are all the other GI features [27].

Just the opposite of other vasculitides, in GPA non-coronary heart disease is more common than coronary heart disease; pericarditis is the most common cardiac manifestation of GPA and other cardiac involvements are including myocarditis, endocarditis, valvulitis, coronary vasculitis (angina pectoris/myocardial infarction), arrhythmias and conduction defects.

Ureteral obstruction, hemorrhagic cystitis, granulomatous prostatitis, urethritis, epididymitis/orchitis and penile necrosis are all genitourinary manifestations of GPA [28].

We have to know that proptosis in conjunction with ENT or lung disease or glomerulonephritis is highly suggestive of the GPA [9, 29].

It also needs to be mentioned that almost all cases with vasculitis including proptosis or sinonasal destruction or saddle-nose deformity or subglottic stenosis are the cases of GPA.

The combination of saddle-nose and subglottic stenosis along with rhinitis and/or nasal ulcer and/or bloody nasal discharge with crusted nose in a patient is compatible with diagnosis of GPA whereas the pure combination of saddle-nose and subglottic stenosis without nasal mucosal ulcer, rhinitis or sinusitis is compatible to Relapsing Polychondritis (RPC). Other causes of saddle-nose deformity are including: Tuberculosis, Leprosy, carcinoma, lymphomatoid granulomatosis, lymphoma, congenital syphilis, cocaine abuse and nasal trauma and surgery [30].

Cell blood count, urine analysis, blood urea nitrogen/creatinine, ESR/CRP, liver function test, Anti-Neutrophil Cytoplasmic Antibody (ANCA) serology, sinuses and lungs imaging and pathology are all paraclinical evaluations that have to be done in a case suspected to be involved in GPA.

ANCA can be checked by Immunofluorescence (IF) assay with more sensitivity and ELISA with more specificity.

We know that upon "IF assay" ANCA has below patterns:

- C-ANCA: cytoplasmic-ANCA
- P-ANCA: perinuclear-ANCA and
- (non-c, non-p) ANCA: atypical-ANCA

The more specific "ELISA method" helps us detect different types of ANCA regarding its substrate including:

- PR3-ANCA: Anti-proteinase 3-ANCA
- MPO-ANCA: Anti-Myeloperoxidase-ANCA
- Others

We know that C-ANCA is usually Anti-PR3 and P-ANCA is usually anti-MPO.

ANCA is positive in 90% of cases with active systemic GPA whereas, it is positive in about 60% of cases with limited GPA. We have to know that about 90% of ANCAs in GPA are C-ANCA and C-ANCAs in GPA are anti-PR3 in about 90% of cases. It needs to be mentioned that the positive predictive values of C-ANCA for GPA are including:

- In systemic disease: < 30%
- In chronic sinusitis: < 15%
- In acute glomerulonephritis: # 98%

As you know ANCA associated vasculitides (AAV) are including:

- Granulomatosis with polyangiitis (GPA)
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA) or Churg-Strauss syndrome (CSS)
- Renal limited vasculitis (RLV)

They have 3 common characters including:

- ANCA positivity
- Small vessel vasculitis (SVV)
- Focal necrotizing pauci-immune glomerulonephritis

It needs to be mentioned that ANCA in other members of AAV e.g. MPA, EGPA and RLV most often is P-ANCA and it is usually anti-MPO.

You know that ANCA positivity is not only seen in AAV but also it can be seen in many other diseases and drugs therapy [31, 32].

Pathologic triad of GPA is including:

- Necrosis
- Granulomatous inflammation and
- Small vessel vasculitis (SVV)

We have to know that granulomatous inflammation can be seen in EGPA too but prolonged history of asthma and blood/tissue eosinophilia in EGPA can distinguish it from GPA.

The absence of granulomatous inflammation in the pathology of MPA and low incidence of ENT involvement (< 30%) in this disease may differentiate it from GPA.

It needs to be mentioned that proptosis, saddle-nose deformity, sinonasal destruction and subglottic stenosis can be seen in GPA but they don't occur in other members of AAV.

The proper sites for biopsy in GPA patients are including:

- ENT (especially sinuses)
- Skin
- Kidney
- Lung

Within ENT we can make a biopsy from nose, ear, sinuses, orbital fossa and so on. The best site for biopsy within ENT is paranasal sinuses whereas the nose is not a good site for biopsy. The nasal sample is small, non-specific or negative for pathologic evaluation of GPA but it is good for rulling out the malignancies and infections involving nose. Skin sample can show leukocytoclastic vasculitis and renal biopsy usually shows focal segmental pauci-immune glomerulonephritis.

Lung biopsy is the best but it is non-accessible and invasive. The positivity of open lung biopsies is more than 90% whereas transbronchial biopsy is positive in less than 10% [33]. The ENT biopsy positivity is about 50% but it is accessible and less invasive.

Upon the clinical/laboratory/imaging judgement of an expert Rheumatologist in cooperation with an expert otolaryngologist and an expert infectious disease specialist the diagnosis of GPA can be established.

Most Rheumatologists can only diagnose the advanced cases of systemic GPA involving ENT, lung and kidney with vasculitic features including palpable purpura, hemorrhagic blister, necrotic ulcers and mononeuritis multiplex along with ANCA positivity and the presence of SVV and granulomatous inflammation in pathology.

But, the cases of limited GPA in early stages without vasculitic features along with ANCA negativity and the absence of SVV and granulomatous inflammation in pathology can only be diagnosed by expert Rheumatologists.

There have been three criteria for GPA including:

- The 1990 ACR classification criteria for Wegener's granulomatosis [34].
- The European Medicine Agency Algorithm (EMA) diagnostic criteria of systemic Granulomatosis with polyangiitis [35].
- Iran criteria for early diagnosis of granulomatosis with polyangiitis [36].

The 1990 ACR classification criteria for Wegener's granulomatosis is including [34]:

- Oral ulcer or bloody/purulent nasal discharge
- Nodule, fixed infiltration or cavity in chest X-Ray
- ≥ 5 RBC with or without RBC cast in urine analysis
- Granulomatous inflammation in pathology

With at least 2 out of above 4 criteria the patient can be classified as a case of Wegener's granulomatosis. It needs to be mentioned that the sensitivity of the 1990 ACR criteria is not enough ($< 80\%$) (36). It can not detect the cases of GPA in early stages and finally it can not make distinction between GPA and MPA. Sometimes by using this criteria the lag period between the initial presentation of GPA and confirmation of it may be a few years.

The EMA criteria has been made only for diagnosis of systemic GPA in the absence of biopsy! It is including [35]:

- Lower airways (chest X-Ray) findings
- Upper airways (ENT) findings
- Glomerulonephritis and
- Positive ANCA

You have to know that for establishment of the diagnosis of GPA all of above items will be needed and its sensitivity is very low.

The Iran criteria for early diagnosis of GPA that is created by the author of this letter is including [36]:

- ENT up to 3 points
- Lung up to 2 points
- Kidney up to 1 point
- ANCA up to 2 points
- Biopsy up to 3 points

In the presence of entry criteria (no other diagnosis upon history and physical examination can better explain the problems) with at least 4 points out of 11 the diagnosis of limited GPA will be established whereas for definite diagnosis of systemic GPA we need at least 5 points out of 11.

We know that with normal/negative pathology and/or negative ANCA, GPA can not be ruled out. With normal ENT or lung or kidney, GPA can not be ruled out either.

Only when all of the organs of ENT, lung and kidney

together are not involved, the diagnosis of GPA will be ignored.

The granulomatous diseases of nose and paranasal sinuses in differential diagnosis of GPA are including [37]:

- Infections: Tuberculosis, Leprosy, Rhinoscleroma, Syphilis, Histoplasmosis, Leishmaniasis, Rhinosporidiosis, Mucormycosis
- Vasculitides: Churg-Strauss syndrome
- Malignancies: Lethal midline granulomatosis, Non keratinizing nasopharyngeal carcinoma.
- Others: Sarcoidosis, cocaine abuse, and so on.

In overall the most important differential diagnosis of limited GPA involved in ENT are Mucormycosis, angiocentric lymphoma and cocaine abuse whereas the most important differential diagnosis of systemic GPA are Mucormycosis, Churg-Strauss syndrome, Microscopic polyangiitis, Sarcoidosis and Tuberculosis.

You have to know that the hyphae of Mucorales is airborne and exists everywhere around us. So, the detection of it within mucosal discharge is not diagnostic. Only the histologic detection of hyphae and positive culture of it can be diagnostic and confirmation of the diagnosis of Mucormycosis needs two steps:

- Step I: Histologic detection of hyphae and
- Step II: Culturable potential of hyphae

Almost all patients with Mucormycosis have an underlying disease as predisposing factor including [38]:

- Advanced, uncontrolled diabetes mellitus
- Ketoacidosis
- Malignancies especially Leukemia/Lymphoma and Myeloproliferative disorders
- Hereditary and/or acquired immunodeficiency states (AIDS)
- Chronic high dose corticosteroid therapy
- Chemotherapy/cytotoxic therapy
- Organ transplantation (especially bone marrow)
- Deferoxamine therapy
- Iron overload/ Hemochromatosis
- IV drug abuse
- Malnutrition
- Burns and so on

We know that one-fifth to one-third of the different population have diabetes mellitus and it is the most common underlying disease for Mucormycosis [39]. The diabetes mellitus can be predisposing factor for Mucormycosis when it is advanced uncontrolled especially when results in ketoacidosis. So a small percentage of the patients with diabetes mellitus involves in Mucormycosis.

I think there is overdiagnosis of Mucormycosis and underdiagnosis of GPA in the world. Many cases of GPA that have been diagnosed by me had previous wrong diagnosis of Mucormycosis ?!

By application of Iran criteria for early diagnosis of GPA only about 50% of our cases with GPA became systemic, due to the earlier diagnosis and management of GPA. Whereas in the world, about 80% of cases with GPA are systemic with kidney involvement.

Despite this achievement the lag period between initial presentation of GPA and the confirmation of diagnosis has been about a few months yet.

Table A: 2017 ACR/EMA revised criteria for too early diagnosis of granulomatosis with polyangiitis (GPA) ^{a,b}

• ENT involvement ^c	Up to 4 points
• Lung involvement ^d	Up to 2 points
• Kidney involvement ^e	1 point
• ANCA Positivity ^f	Up to 2 points
• Biopsy findings ^g	Up to 2 points

a. Entry criteria: no other prominent diagnosis such as tuberculosis, EGPA (CSS), MPA, mucormycosis, cocaine abuse, RPC, etc can explain the condition according to the patient’s history and physical examination.

b. The definite diagnosis of limited GPA (ENT and/or Lung involvement) can be established if the patient fulfills ≥ 4 points out of 11, whereas with at least 5 points out of 11 the diagnosis of systemic GPA [(ENT and/or Lung) along with Kidney involvement] will be defined.

c. ENT points: More than one episode of bloody nasal discharge with nasal crusting or nasal ulcer or severe nasal pain: 1 point. Oral necrotic ulcer: 1 point or strawberry gum hyperplasia: 2 points totally up to 2 points for oral cavity. Persistent or recurrent or intractable sinusitis: 1 point. Persistent or recurrent or intractable or bilateral otitis media or otitis media with sensory-neural hearing loss: 1 point. Proptosis: 2 points. Saddle-nose deformity: 2 points. Subglottic stenosis: 2 points. In PNS CT scan: pansinusitis or sinus mass: 1 point. Sinonasal destruction: 2 points. Mastoiditis: 1 point. Attention please: if sinusitis is repeated in both history/physical examination and PNS CT scan just PNS CT scan score is acceptable.

d. Lung points: hemoptysis: 1 point. In CXR or HRCT: nodule: 2 points. cavity: 2 points. fixed infiltration: 1 point.

e. Kidney points: hematuria (≥ 5 RBC or > +1 blood) or proteinuria (>+1) or RBC cast: 1 point.

f. ANCA points: positive ANCA or P-ANCA or Anti MPO-ANCA: 1 point. positive C-ANCA or Anti-PR3-ANCA: 2 points.

g. Biopsy points: small vessel vasculitis without eosinophilia: 1 point. granulomatous inflammation without eosinophilia: 2 points.

Table B: Practical Guideline approaching towards the diagnosis of GPA.

Step I - History and physical examination by Rheumatologist and otolaryngologist - CBC, Blood urea nitrogen/creatinine, ESR, Urinary analysis, ANCA serology, Liver function test - Sinuses X-Ray, Chest X-Ray
Step II - CT-scan of sinuses (PNS CT) - HRCT of lungs
Step III - ENT endoscopy especially of sinuses - ENT biopsy especially of sinuses
Step IV - Other sites biopsy ➤ Skin ➤ Kidney ➤ Lung: especially Thoracoscopy or open thoracotomy

References

1. Tarzi RM, Pusey CD. Current and future prospects in the management of granulomatosis with polyangiitis (Wegener's granulomatosis). *Therapeutics and Clinical Risk Management*. 2014; 10:279-293. doi:10.2147/TCRM.S41598.
2. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37:187.
3. Falk RJ, Gross WL, Guillevin L, et al. Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. *Arthritis Rheum* 2011; 63:863.
4. Salehi-Abari I, Khazaeli S, Zarandy MM, et al. Early Evaluation of Granulomatosis with Polyangiitis (Wegener's) in the Patients with Atypical Sinusitis: An Introduction to Amir Alam Hospital Recommendation for Early Detection of Granulomatosis with Polyangiitis in Sinusitis. *Rheumatol Curr Res*.2012; 2:110.
5. Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. The Glomerular Disease Collaborative Network. *Ann Intern Med* 1990; 113:656.
6. Paddock M, Lynch C, Paska L; Wegener's granulomatosis in primary care. *JRSM Short Rep*. 2010; 1(7):59.
7. Knopf A, Chaker A, Stark T, et al. Clinical aspects of granulomatosis with polyangiitis affecting the head and neck. *Eur Arch Otorhinolaryngol*. 2015;272(1):185-93
8. Fowler NM, Beach JM, Krakovitz P, Spalding SJ. Airway manifestations in childhood granulomatosis with polyangiitis (Wegener's). *Arthritis Care Res (Hoboken)*. 2012; 64(3):434-40.
9. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med*. 1992; 116(6):488-98.
10. Ferguson BJ. Acute and chronic sinusitis. How to ease symptoms and locate the cause. *Postgrad Med*. 1995; 97(5):45-8, 51-2, 5-7.
11. Kempf HG. Ear involvement in Wegener's granulomatosis. *Clin Otolaryngol Allied Sci*. 1989; 14(5):451-6.
12. Pichichero ME. Recurrent and persistent otitis media. *Pediatr Infect Dis J*. 2000; 19(9):911-6.
13. Amiraraghi N, Robertson S, Iyer A. Primary otological manifestations of granulomatosis with polyangiitis: a case series. *J Laryngol Otol*. 2015 Feb; 129(2):179-82.
14. Aravena V, Beltrán V, Cantín M, Fuentes R. Gingival hyperplasia being the first sign of Wegener's granulomatosis. *International Journal of Clinical and Experimental Medicine*. 2014; 7(8):2373-2376.

15. Harper SL, Letko E, Samson CM, et al. Wegener's granulomatosis: the relationship between ocular and systemic disease. *J Rheumatol* 2001; 28:1025.
16. Fechner FP, Faquin WC, Pilch BZ. Wegener's granulomatosis of the orbit: a clinicopathological study of 15 patients. *Laryngoscope* 2002; 112:1945.
17. Schmidt J, Pulido JS, Matteson EL. Ocular manifestations of systemic disease: antineutrophil cytoplasmic antibody-associated vasculitis. *Curr Opin Ophthalmol* 2011; 22:489.
18. Girard C, Charles P, Terrier B, et al. Tracheobronchial Stenoses in Granulomatosis With Polyangiitis (Wegener's): A Report on 26 Cases. *Pilar BZ, ed. Medicine*. 2015;94(32).
19. Bohm M, Gonzalez Fernandez MI, Ozen S, et al. Clinical features of childhood granulomatosis with polyangiitis (wegener's granulomatosis). *Pediatr Rheumatol Online J*. 2014;12:18.
20. Rosenberg DM, Weinberger SE, Fulmer JD, Flye MW, Fauci AS, Crystal RG. Functional correlates of lung involvement in Wegener's granulomatosis. Use of pulmonary function tests in staging and follow-up. *Am J Med*. 1980;69(3):387-94.
21. Martinez F, Chung JH, Digumarthy SR, et al. Common and Uncommon Manifestations of Wegener Granulomatosis at Chest CT: Radiologic-Pathologic Correlation. *RadioGraphics* .2011; 32(1).
22. Renaudineau Y, Le Meur Y. Renal involvement in Wegener's granulomatosis. *Clin Rev Allergy Immunol*. 2008 ;35(1-2):22-9.
23. Andrassy K, Erb A, Koderisch J, Waldherr R, Ritz E. Wegener's granulomatosis with renal involvement: patient survival and correlations between initial renal function, renal histology, therapy and renal outcome. *Clin Nephrol*. 1991;35(4):139-47.
24. Watts RA. ANCA-associated vasculitis. *Arthritis Research UK*. 2012;1.
25. Daoud MS, Gibson LE, DeRemee RA, et al. Cutaneous Wegener's granulomatosis: clinical, histopathologic, and immunopathologic features of thirty patients. *J Am Acad Dermatol* 1994; 31:605.
26. Holle JU, Gross WL. Neurological involvement in Wegener's granulomatosis. *Curr Opin Rheumatol*. 2011;23(1):7-11.
27. 42.Pagnoux C, Mahr A, Cohen P, Guillevin L. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine (Baltimore)* 2005; 84:115.
28. Davenport A, Downey SE, Goel S, Maciver AG. Wegener's granulomatosis involving the urogenital tract. *Br J Urol*. 1996;78(3):354-7.
29. Tarabishy AB, Schulte M, Papaliodis GN, Hoffman GS. Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. *Surv Ophthalmol*. 2010;55(5):429-44.
30. Sachse F, Stoll W. Nasal surgery in patients with systemic disorders. *GMS Current Topics in Otorhinolaryngology, Head and Neck Surgery*. 2010;9.
31. Rao JK, Weinberger M, Oddone EZ, Allen NB, Landsman P, Feussner JR. The role of antineutrophil cytoplasmic antibody (c-ANCA) testing in the diagnosis of Wegener granulomatosis. A literature review and meta-analysis. *Ann Intern Med*. 1995;123(12):925-32.
32. Choi HK, Liu S, Merkel PA, Colditz GA, Niles JL. Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitides: metaanalysis with a focus on antimyeloperoxidase antibodies. *J Rheumatol*. 2001; 28(7):1584-90.
33. Travis WD, Hoffman GS, Leavitt RY, Pass HI, Fauci AS. Surgical pathology of the lung in Wegener's granulomatosis. Review of 87 open lung biopsies from 67 patients. *Am J Surg Pathol*. 1991;15(4):315-33.
34. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990; 33:1101.
35. 8.Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2007; 66:222.
36. Salehi-Abari I, Khazaeli S, Khak M, Motesaddi Zarandy M, Hasibi M. Early diagnosis of granulomatosis with

- polyangiitis: An introduction to the newly designed Iran criteria. *Indian Journal of Rheumatology*. 2013;8(3):107-11.
37. Fuchs HA, Tanner SB. Granulomatous disorders of the nose and paranasal sinuses. *Curr Opin Otolaryngol Head Neck Surg*. 2009;17(1):23-7.
38. Bouza E, Munoz P, Guinea J. Mucormycosis: an emerging disease? *Clin Microbiol Infect*. 2006;12:7-23.
39. Petrikos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012;54 Suppl 1:S23-34.